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# INTERSTITIAL LUNG DISEASES AND THE PNEUMOCONIOSES:

**What's Important For You to Know?**

- **How do interstitial lung diseases (ILD) differ from pneumonia?**
- **Many ILD have a wide clinical spectrum of presentation and progression.**
- **Most ILD are "restrictive" but some have an "obstructive" component.**
- **Variable pathology pattern: granulomatous vs. non-granulomatous.**
- **Clinically and radiographically, most ILD behave similarly.**
- **Most ILD have the potential to progress to interstitial pulmonary fibrosis.**
- **Pay attention to: sarcoidosis, hypersensitivity pneumonitis and idiopathic pulmonary fibrosis.**
- **Pneumoconioses are ILD caused by mineral dusts (sites of lung involvement and carcinogenic potential of the dusts are different).**
- **Cytokines, oxygen radicals and reactive nitrogen species play a pathogenetic (i.e., mechanistic) role in all the pneumoconioses.**
- **Pay attention to: silicosis, coal worker's pneumoconiosis, asbestosis, pleural plaques and malignant mesothelioma.**

**Case Study:** A 63-year-old construction worker was complaining of a dry cough and progressive breathlessness, especially on climbing stairs. He had quit smoking (1 pack/day for 12 years) 15 years previously. Chest examination disclosed bibasilar fine, end-inspiratory crackles, and a chest X-ray showed focal pleural thickening with bilateral irregular opacities in both lower lung zones. PFT's showed an $FEV_1$ that was 57% of the predicted value, an $FEV_1$ : FVC ratio that was 92%, and a TLC that was 70% of that predicted. The $DL_{CO}$ was 76% of the predicted value.

**Interstitial Lung Diseases:** The term, *"interstitial lung disease,"* refers to any of more than 180 disorders characterized by injury to the interstitial compartment of the lung. In general, interstitial lung diseases are characterized by the following:

- These disease processes usually have a prominent component of ***interstitial pneumonitis*** (***alveolitis***) — macrophages, lymphocytes, neutrophils and/or eosinophils. These features are non-specific for many ILD's.
- There is a variable component of endothelial and alveolar epithelial injury.
- Intra-alveolar "spillover" is rare — this is seen most prominently in a histologic variety of interstitial lung disease known as ***desquamative interstitial pneumonitis*** (***DIP***).
- Many forms of interstitial lung disease terminate in ***diffuse interstitial pulmonary fibrosis*** → "end-stage" lung disease, with the development of so-called ***"honeycomb lung."***

**Etiology of Interstitial Lung Diseases:** The interstitial lung diseases comprise a heterogeneous group of disorders which have no uniformity regarding classification and terminology. They are best categorized into those of **unknown causation** (**idiopathic**) and those of **known causation**. Although ILD may be classified in different ways, they are best classified according to their etiology:

| Known Causes of ILD | Idiopathic ILD |
|---|---|
| ● Occupational & environmental (e.g., silica, asbestos, coal dust, beryllium)<br>● Organic dusts (hypersensitivity pneumonitis)<br>● Gases, fumes & aerosols (e.g., $O_2$ toxicity, $SO_2$, toluene)<br>● Drugs (cyclophosphamide, busulfan, bleomycin, nitrofurantoin, amiodarone, paraquat, methotrexate)<br>● Heroin abuse<br>● Radiation<br>● Infections (influenza, CMV, *Mycobacterium tuberculosis*, *Pneumocystis carinii*) | ● Sarcoidosis<br>● Idiopathic pulmonary fibrosis<br>● Autoimmune & collagen-vascular disorders (rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Wegener's granulomatosis, Goodpasture's syndrome)<br>● Bronchocentric granulomatosis<br>● Idiopathic pulmonary hemosiderosis<br>● Chronic eosinophilic pneumonia<br>● Histiocytosis X<br>● Pulmonary alveolar proteinosis<br>● Lymphangioleiomyomatosis<br>● Amyloidosis |

**Hypersensitivity Pneumonitis:** This comprises a spectrum of immunologically-mediated interstitial lung disorders caused by intense or prolonged exposure to organic dust allergens. It is important to recognize these diseases early in their course, since progression to pulmonary fibrosis can be prevented by removal of the offending allergens. These allergens include the spores of thermophilic bacteria (which grow optimally at 50-60° C), true fungi, animal proteins or bacterial products:

- **Farmers' lung** — inhalation of thermophilic actinomycetes spores in humid, moldy hay.
- **Pigeon breeder's lung** — inhalation of proteins from birds' sera, excreta and feathers.
- **Humidifier lung** — inhalation of thermophilic bacteria in heated water reservoirs.
- **Byssinosis** — inhalation of cotton, linen, and/or hemp in the textile industry.
- **Bagassosis** — inhalation of compressed sugar cane (bagasse).

**Clinical Features of Hypersensitivity Pneumonitis:** The clinical manifestations are variable:

- **Acute phase:** Repeated acute attacks follow inhalation of dust allergens by sensitized patients → symptoms appear within ± 4-6 hours, and remit within ± 24-48 hours. Affected patients present with cough, fever, chills and dyspnea.

Diffuse and nodular infiltrates are noted on chest radiographs, and patients manifest a ***restrictive pulmonary function test profile***. Most patients have detectable ***serum IgM and IgG precipitins*** against offending allergens. Some studies have shown that specific allergens can induce lymphoid mitogenesis and cytokine secretion by patients' blood lymphocytes. On this basis, hypersensitivity pneumonitis is believed to represent an ***immune complex-mediated, type III hypersensitivity reaction*** (seen mainly in the **acute phase**) as well as a ***type IV-delayed hypersensitivity reaction*** (especially in the **chronic phase**). However, the majority of individuals who have serum precipitins against inhaled antigens do <u>not</u> develop hypersensitivity pneumonitis after exposure to these allergens. Thus, it is conceivable that patients who develop the disease have a genetic predisposition towards it. **Patients generally demonstrate a good response to steroids**.

- **Chronic phase:** This follows continued and protracted exposure to offending allergens. Affected patients develop progressive respiratory failure → hypoxemia, dyspnea, and cyanosis. Pulmonary function tests show a ***mixed restrictive and obstructive pattern***. **Patients do not respond to steroids in the chronic phase, due to development of end-stage pulmonary fibrosis.**

**<u>Pathologic Features of Hypersensitivity Pneumonitis</u>:**

- ***Interstitial pneumonitis***, characterized by lymphocytes, foamy macrophages and plasma cells.
- Multiple, ***non-caseating granulomas*** comprising epithelioid cells and giant cells.
- An ***intra-alveolar infiltrate***.
- ***Obliterative bronchiolitis*** → produces an ***obstructive pulmonary function profile*** (especially during the chronic phase).
- **Interstitial pulmonary fibrosis** develops in the chronic phase.

**<u>Sarcoidosis</u>:** This disease represents a multisystem disorder of unknown etiology which is characterized by ***non-caseating granulomas composed of epithelioid cells with or without Langhans giant cells***. Bilateral hilar lymphadenopathy and/or lung involvement are common ($\pm$ 95% of cases). Histologically, sarcoidosis is characterized by a ***diffuse interstitial pneumonitis*** (an entity which has been referred to as ***"alveolitis"***). Other affected organs include:

- Hilar lymph no*des* → ***lymphadenopathy*** ($\pm$ 75% of cases).
- *Eyes* (**uveitis**) and parotid glands (***parotitis***) → dry secretions. If there is uveo-parotid involvement, this entity is known as ***Mikulicz's syndrome***.
- Liver and spleen → ***hepatosplenomegaly***.
- Skin, bone marrow, heart, nervous system, kidneys, joints, and endocrine organs.

**<u>Pathogenesis of Sarcoidosis</u>:** Despite an exhaustive search, no etiologic agent has definitively been implicated in sarcoidosis. There is also no suitable animal model for studying the pathogenesis of sarcoidosis. However, ***examination of bronchoalveolar lavage* (*BAL*) samples** from sarcoid patients suggests that the disease represents an exaggerated immunologic response to an undefined antigen:

- Sarcoid patients have greatly increased numbers of bronchoalveolar CD4 +ve T-cells and alveolar macrophages compared with normal individuals.
- Affected patients' BAL cells also manifest ↑ secretion of certain cytokines (IL-1, IL-6, and TNF-$\alpha$).
- Alveolar macrophages from sarcoidosis patients demonstrate enhanced MHC class II antigen expression.
- Increased levels of IL-2 receptors are noted in BAL samples and serum from sarcoid patients.
- Some patients have increased circulating $\gamma\delta$ receptor +ve T-cells (also seen in TB patients) – ? represents a response to undefined mycobacterial antigen(s).

**Clinical Features of Sarcoidosis:** This disease may affect both sexes, all ages, and all races. However, it is about 10-15 times more common in blacks than whites, and black females (aged 20-40 years) are especially prone to develop sarcoidosis and tend to have a more aggressive form of the disease. In contrast, sarcoidosis is rare among Chinese and Greeks. Although no clear-cut genetic susceptibility has been shown in sarcoidosis, some clinical studies have demonstrated associations of certain HLA antigens with some clinical subtypes: the HLA-B8, HLA-DR3 phenotype has been shown to be associated with an acute form of sarcoidosis (Löfgren's syndrome), whereas HLA-B13 has been shown to be associated with a chronic, persistent form of sarcoidosis. The clinical presentation is varied:

- ± 50-60% of cases are ***asymptomatic*** — are diagnosed on chest radiography or lymph node biopsy.
- ± 40% of cases have ***constitutional symptoms*** — fever, weight loss, fatigue and malaise.
- The chest radiographic appearances of sarcoidosis are varied. Thus, some patients manifest bilateral hilar lymphadenopathy. This may be very prominent, hence the term, ***"potato nodes."*** If there is pulmonary involvement, this produces patchy X-ray densities due to alveolitis or interstitial fibrosis.
- ± 20-25% of cases have impaired pulmonary function — a ***restrictive pattern*** is usual, but some cases also have an ***obstructive pattern*** (involving small and large airways).
- **No single laboratory test is diagnostic of sarcoidosis!**
- ± 10% of cases have ***hypercalcemia*** (due to increased synthesis of 1,25-$\{OH\}_2$-vitamin $D_3$ in sarcoid granulomas).
- The detection of ***non-caseating granulomas*** by either **transbronchial biopsy** (via a fiberoptic bronchoscope) or **mediastinal lymph node biopsy** (via mediastinoscopy) is the hallmark for the diagnosis of sarcoidosis.
- Many patients with active sarcoidosis have an ***elevated serum angiotensin***

converting enzyme (*ACE*) level and **gallium-67 lung scans** *show* ***enhanced gallium uptake***.

- Many patients have ***cutaneous anergy to skin test antigens*** associated with ***hyper-γ-globulinemia*** and ***circulating immune complexes*** in their sera.
- The technique of **bronchoalveolar lavage** demonstrates ***increased numbers of helper T cells*** (***CD2/CD4 +ve phenotype***), whereas the **peripheral blood** has ***decreased proportions of helper T cells*** *and* ***increased proportions of suppressor T cells*** (***CD2/CD8 +ve phenotype***).
- Sarcoidosis therefore represents another example of a ***mixed, type III and type IV hypersensitivity reaction***.
- Historically, ± 80% of sarcoid patients were shown to manifest a ***positive Kveim test*** → an epithelioid cell granuloma developed ± 6 weeks after intradermal injection of a splenic extract from a sarcoidosis patient. **This test is no longer used, since it is poorly standardized**!

**<u>Idiopathic Pulmonary Fibrosis (IPF)</u>:** This entity, which is referred to in the British and European literature as ***cryptogenic fibrosing alveolitis***, is a disease of unknown etiology. It is characterized, in the early phases, by a ***diffuse interstitial pneumonitis*** which frequently progresses to ***interstitial pulmonary fibrosis***. Idiopathic pulmonary fibrosis may occur at any age, but most commonly afflicts the 50-60 year age group with a slight male preponderance. ± 40% of patients experience an antecedent "flu-like" illness. Genetic factors may play a role, since an increased frequency of HLA-B8, HLA-B12, HLA-B15, and HLA-DR2 antigens has been found among afflicted patients when compared with the general population. **± 20% of idiopathic pulmonary fibrosis patients have associated systemic autoimmune diseases**, (i.e., ***systemic lupus erythematosus***, ***rheumatoid arthritis***, and ***scleroderma***).

**<u>Pathogenesis of IPF</u>:** Although the exact pathogenetic mechanisms have not been precisely elucidated, IPF is considered to represent a stereotypic inflammatory response of the alveolar wall to sequential injuries of different type, duration, and intensity. Conceivably, repeated injury to type I pneumocytes results in an **alveolitis** characterized by interstitial edema and accumulation of inflammatory cells within the alveolar septa. **There is some evidence that immune mechanisms may trigger these events**, since high levels of ***immune complexes*** have been demonstrated in patients' serum and BAL specimens. Also, ***granular deposits of IgG have been detected by immunofluorescence in the alveolar septa*** of **biopsy specimens**. As IPF progresses, type II pneumocytes regenerate, in an attempt to repair the defect, with resultant type II cell hyperplasia. Ultimately, there is ***organization of the lesion***, with fibroblasts proliferating within the intra-alveolar and septal exudates, and culminating in obliterative fibrosis of the alveolar architecture. The cytokines, connective tissue growth factor (CTGF) and TGF-β, are believed to play key roles in mediating lung fibrosis. Continual remodeling of the abnormal collagen framework eventually produces a ***honeycomb lung***, in which there are numerous, small cysts separated by dense, fibrous septa. It should be noted that ***the alveolitis of IPF is non-specific*** and is common to many ILD.

**<u>Pathology of IPF</u>:** The characteristic histologic lesions in IPF are so-called ***fibroblastic foci*** comprising myofibroblasts and extracellular matrix material. Elsewhere, there is a variable interstitial inflammatory response composed mainly of lymphocytes with occasional neutrophils, eosinophils, plasma cells, or macrophages. This is referred to as ***usual interstitial pneumonitis (UIP)***.

**<u>Clinical features of IPF</u>:** Since idiopathic pulmonary fibrosis represents a spectrum of disease (***UIP* vs. *honeycomb lung***), patients exhibit varying degrees of respiratory difficulty:

- UIP patients experience gradual onset of *dry cough and exertional dyspnea* over <u>+</u> 3-6 years. However, the median survival is < 3 years.
- On chest auscultation, ***late inspiratory crackles* (*rales*)** are heard.
- Chest radiographs display bilateral, lower lobe ***"ground-glass" infiltrates***.
- In the late stages, patients develop ***arterial hypoxemia, pulmonary hypertension, cor pulmonale,*** and ***clubbing of the digits***.
- A small subgroup of patients develop a rapid onset, fulminant variety of interstitial pneumonitis and pulmonary fibrosis, an entity known as ***Hamman-Rich syndrome***. **Thus, the term, *idiopathic pulmonary fibrosis*, should <u>not</u> be used synonymously with *Hamman-Rich syndrome*, except in rare circumstances**.
- **Patients with *DIP* tend to respond to steroid therapy**.

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**<u>The Pneumoconioses</u>:** The term, ***pneumoconiosis***, is derived from two Greek words: πνευμων (meaning *lung*) and κονισ (meaning *dust*). Accordingly, "pneumoconiosis" should be regarded as a generic term for any disease of the lung caused by the inhalation of dust particles. Broadly speaking, the pneumoconioses should include the pulmonary tissue responses to inhaled mineral (i.e., inorganic) and organic (e.g. bacterial or fungal protein) dusts. However**, it is currently generally accepted that the pneumoconioses should be restricted to the pathologic effects of inhaled <u>mineral dusts</u> in the lungs**. Thus, hypersensitivity pneumonitis and the pneumoconioses should be regarded as separate and distinct dust diseases of the lung. It should be noted that the pneumoconioses are essentially diseases of insidious progression and long clinical latency (i.e., the diagnosis can only be established many years after initial contact with the offending dust).

**<u>Factors Determining the Biologic Effects of Mineral Particles</u>:** The intrapulmonary biologic effects of inhaled mineral particles are dependent upon a variety of factors. These include:

- **Size and shape of the particles:** Only a tiny proportion of inhaled dust particles are respirable (i.e., capable of reaching the alveolar spaces). This stems from the fact that larger particles (i.e., > 5 µm in diameter impact preferentially in the more proximal parts of the respiratory tract (e.g., the nose and pharynx) and within the airways (where there is some impedance to air flow). Consequently, the larger, heavier dust particles tend to settle proximal to the respirable portions of the lung (i.e., proximal to the respiratory bronchioles). Only particles < 5 µm in diameter are respirable. Those particles which are arrested within the airways are continually being removed more proximally by the conveyor-belt action of the "muco-ciliary escalator" (which lines the surfaces of the trachea, bronchi and bronchioles). As a consequence, most inhaled particles are eventually swallowed or expectorated.

  Particles may vary not only in diameter but also in length. Those particles which are longer than they are wide are called "fibers" (i.e., they have a length-to-width aspect ratio of 3 : 1 or greater). Although most mineral dust particles are non-fibrous (e.g., silica, carbon, coal dust and beryllium), **there are some important fibrous dusts (e.g., asbestos, talc, zeolite, fiberglass and synthetic wool)**. It should be noted that **the aerodynamic properties and respirability of fibers are governed by their diameter and <u>not</u> their length**. Thus, a fiber of 100 µm in length (but only 1 µm in diameter) is still capable of traversing the alveolar region of the lung.

- **Duration of exposure to the dust:** As a general rule, there is usually a good correlation between the clinico-pathologic severity of a pneumoconiosis and the total cumulative dose of the offending dust inhaled. The duration of mineral dust exposure (which usually occurs over many years in most occupational or industrial settings) frequently provides a crude clinical index of the total cumulative dose inhaled.

- **Amount of dust retained in the lungs:** Although this factor will, naturally, be influenced by the total cumulative dose inhaled, the intrapulmonary mineral dust burden is dependent upon the efficacy of the normal homoeostatic clearance mechanisms of the lungs. Thus, many respirable particles or fibers are phagocytized by alveolar macrophages and eventually cleared from the lungs via the muco-ciliary escalator. Other particulates penetrate the lining of the alveoli and the respiratory bronchioles, where they are engulfed by interstitial macrophages, or else they may drain via regional lymphatics to subpleural and hilar lymph nodes. It should be noted that pulmonary clearance can be impaired in some people (e.g., in cigarette smokers, alcoholics, and patients with lung cancer, infection and cystic fibrosis).

- **Cytotoxic potential of the mineral dust:** Some mineral dusts (e.g., carbon pigment, diamond dust and zirconium) are biologically inert. By contrast, other particulates (e.g., ***quartz***, ***cristobalite*** and ***asbestos***) are intrinsically cytotoxic to alveolar macrophages and are also capable of inducing pulmonary fibrosis. Biologic activity appears to be a function of the crystalline structure, surface properties and solubility of mineral dusts.

- **Host susceptibility:** Not everyone who is exposed to a toxic mineral dust (e.g., ***silica*** or ***asbestos***) will develop pulmonary fibrosis. Clearly, certain ill-defined "host susceptibility" factors also appear to play a role in the pathogenesis of the pneumoconioses. Some of these may govern the rate of pulmonary clearance of particulates. It is possible that genetic factors may also play a role in this regard, since some pneumoconioses (e.g., ***asbestosis***) may occur in successive generations of families who work in industrial settings. **The pneumoconioses will only develop when the natural "host defenses" are overwhelmed by a heavy burden of inhaled mineral dust**.

**Anatomic Sites Affected by the Pneumoconioses:** Since the pneumoconioses characteristically affect the lung interstitium, they constitute examples of **ILD**. The fibrogenic varieties of mineral dusts all produce *interstitial pulmonary fibrosis*. The fibrosis is evident as characteristic chest X-ray opacities and is associated with a *"restrictive" pulmonary function test profile*. The lesions all commence in the regions where respirable dusts impact in the lungs, namely the respiratory bronchiole bifurcations (especially the first and second order of respiratory bronchioles).

**Pneumoconioses Due to Non-fibrogenic Dusts:** This group of conditions is characterized by exposure to non-toxic or inert mineral dusts, such as:

- Iron — which produces *siderosis*.
- Carbon — *anthracosis*.
- Barium — *baritosis*.
- Tin — *stannosis*.
- Antimony.
- Zirconium.

These diseases are all characterized by focal accumulations of the offending mineral dust within alveolar and interstitial macrophages. Anthracosis is especially common amongst city dwellers and cigarette smokers. Exposure to those mineral dusts which have a high atomic number (i.e., an atomic number > 12) is associated with spectacular nodular chest X-ray densities. These diseases are, however, essentially asymptomatic and are not characterized by pulmonary fibrosis.

**Silicosis: This disease occurs in occupations where crystalline silica (i.e., silicon dioxide) is inhaled**. This happens when silica-containing rock is crushed (e.g., in the occupational settings of stonemasons, iron and steel workers, granite workers, diatomite workers, ceramic workers, foundry workers, sandblasters and hardrock, gold, tin and copper miners). There are five naturally-occurring crystalline forms of silica (quartz, cristobalite, tridymite, stishovite and flint). Of these, quartz and, to a much lesser extent, cristobalite, constitute major clinical hazards. It should be noted that silica can also occur as a natural contaminant of other mineral dusts (e.g., coal dust).

**Types of Silicosis:**

- **Acute:** This is an unusual reaction to silica which follows exposure to high levels of small particle-sized silica over a relatively short time (i.e., 1-3 years). Histologically and ultrastructurally the disease resembles pulmonary alveolar proteinosis. The alveoli are filled with lipoproteinaceous debris and there is an accompanying alveolar septal mononuclear inflammatory infiltrate. There is frequently an overlying fibrinous pleuritis. This is a serious disease, with patients experiencing severe dyspnea, which may progress to ***acute cor pulmonale***.

- **Chronic: This is the more common variety of silicosis**. Patients' symptoms usually develop approximately 20-40 years after initial silica exposure and may occur after occupational exposure has ceased. Chronic silicosis comprises a variety of pulmonary reactions to inhaled silica:

  ■ **Simple silicosis:** This is characterized by the development of multiple **silicotic nodules** within the lung parenchyma and within regional lymph nodes. These nodules are usually 1-2 mm in diameter and produce characteristic X-ray opacities. Patients' chest X-ray films exhibit a so-called "snowstorm" appearance. Histologically, the silicotic nodule has an acellular, fibrous core with a hyalinized center composed of concentric rings of collagen. The nodule is surrounded by macrophages, lymphocytes, plasma cells and fibroblasts. **Birefringent silica particles are seen within the nodule, using a polarizing filter**. Silicotic nodules are especially prominent in the upper lobes of the lungs and they tend to follow sites of lymphatic drainage (e.g., subpleural and hilar regions as well as the tracheobronchial nodes). Simple silicosis is frequently asymptomatic.

  ■ **Complicated silicosis:** This term refers to the coalescence of silicotic nodules, to form larger aggregates. It is often symptomatic.

  ■ **Progressive massive fibrosis. Conglomerate masses greater than 3 cm in diameter are referred to as progressive massive fibrosis (PMF)**. It is characterized histologically by a dense, hyaline, amorphous area of fibrosis without concentric laminations. It is associated with severe symptoms. PMF is not specific for silicosis and may occur with other pneumoconioses. It should be regarded as a progressive, disabling form of severe interstitial pulmonary fibrosis which frequently progresses to respiratory failure.

■ **Tuberculo-silicosis:** Silicotic patients have an increased susceptibility to mycobacterial infections (either *Mycobacterium tuberculosis* or *M. kansasii*). **Caseation is prominent in these lesions**, but a granulomatous response is minimal. This may relate to compromised macrophage function due to the inhalation of silica particles.

■ **Caplan's syndrome: This refers to the association of *rheumatoid arthritis* (an autoimmune disease) with any *pneumoconiosis*.** Histologically, the features of a **rheumatoid nodule** (i.e., central necrosis surrounded by palisading macrophages and a rim of plasma cells and lymphocytes) are superimposed on those of a **silicotic nodule**.

■ **Interstitial pneumonitis:** This is an early response of the lungs to many mineral dusts. It is characterized by a lympho-mononuclear alveolar septal infiltrate and by intra-alveolar accumulations of alveolar macrophages.

**<u>Clinical Features of Silicosis</u>:** The clinical manifestations of exposure to silica dust are variable and dependent on the severity of the underlying lesions:

- Simple silicosis is usually asymptomatic. Frequently, the silicotic nodules are detected incidentally, on X-ray or at autopsy.
- Symptoms develop relatively early (often within less than 10 years after initial silica exposure) in patients with PMF, as evidenced by chronic cough, dyspnea and infection.
- Impaired carbon monoxide gas diffusion ($DL_{CO}$) pattern.
- Cor pulmonale is a rare complication.

**<u>Immunologic Reactions in Silicosis</u>:** There is some evidence that immunologic mechanisms may play a role in the pathogenesis of silicosis:

- Silicotic nodules are surrounded by macrophages, lymphocytes and plasma cells.
- IgG and IgA are detectable within silicotic nodules.
- Silicotic patients have high serum titers of autoantibodies (anti-nuclear factors and rheumatoid factors).
- Silica-containing alveolar macrophages secrete increased amounts of IL-1, TNF-$\alpha$, TGF-$\beta$, fibronectin, PDGF and IGF-1. All of these substances stimulate fibroblast proliferation *in vitro* (i.e., they act as ***growth factors***).
- ***Silica is toxic to macrophages***. When ingested by macrophages, it forms covalent bonds with phosphate esters of the cell membrane. The resultant injury to phagolysosomal membranes results in "leakage" of lysosomal enzymes from the macrophage. This produces tissue injury. Additionally, toxic oxygen radicals are thought to play a role in this regard, since alveolar macrophages from silicotic patients secrete increased amounts of superoxide anion and $H_2O_2$.
- There is also an increased incidence of certain **autoimmune diseases** in

silicosis, especially **systemic lupus erythematosus**, **rheumatoid arthritis** and **scleroderma**.

**<u>Silica and Lung Cancer</u>:** There is some evidence, based upon epidemiologic studies, that silica is a lung carcinogen. However, lung cancer only appears to supervene among gold miners who have pre-existent silicosis. Thus, silica-related lung cancer appears to be a form of so-called scar cancer.

**<u>Coal Workers' Pneumoconiosis (CWP)</u>:** This term refers to the pulmonary reaction to inhaled coal dust (which is a complex mixture of elemental carbon, silica, various organic compounds, metals and minerals). The effects of coal dust inhalation are the following:

- **<u>Simple CWP</u>:** This is characterized by the presence of coal dust macules and coal dust nodules, which are found in about 25-90% of coal miners. The macules vary in size from about 0.1-1.0 cm in diameter and are more frequent in the upper lobes. They are not palpable lesions. By contrast, the nodules are larger (i.e., 1-2 cm in diameter) and have a firm consistency. Histologically, both lesions comprise accumulations of alveolar macrophages (especially around respiratory bronchioles) which are filled with jet-black anthracotic pigment. Only the coal nodules, however, contain a central area of irregular fibrosis which has a stellate configuration. There is frequently an adjoining zone of focal or centrilobular emphysema.

- **Progressive massive fibrosis (complicated CWP):** This resembles the PMF of silicosis and usually afflicts the upper lobes. The fibrosis is irregular and haphazard. Although the pathogenesis of PMF is poorly understood, the following factors are believed to play a role:
  - High quartz content of the coal dust.
  - High total burden of lung dust.
  - Associated pulmonary infections (e.g., histoplasmosis and tuberculosis).
  - Obliterative pulmonary vascular lesions.
  - Immunologic mechanisms. CWP patients have elevated levels of IgA in the lungs and in serum. Furthermore, many CWP patients have serum autoantibodies detectable against pulmonary antigens.

- **Caplan's syndrome.**

- **Industrial bronchitis:** This lesion is non-specific and resembles the chronic bronchitis of cigarette smokers.

- **Gastric carcinoma:** There is a predisposition towards gastric cancers among coal workers. This may possibly relate to swallowed carcinogens (e.g., *polycyclic aromatic hydrocarbons*) in coal dust.

**Clinical Features of CWP:** These are similar, in certain respects, to those of silicosis:

- Benign CWP is essentially asymptomatic, although characteristic X-ray opacities are seen, which produce a "tattooing effect".
- CWP patients with PMF tend to cough up jet-black anthracotic sputum (a phenomenon called *melanoptysis*). These patients also experience progressive dyspnea, cyanosis, and pulmonary infections. Irregular opacities are noted on their chest X-rays. The disease may progress to *cor pulmonale*.

**Asbestos-Related Diseases:** *Asbestos* is a generic term for a group of ubiquitous, naturally-occurring fibrous silicates. There are two main geologic varieties of asbestos: serpentine (which has a softer, curly configuration) and amphibole (which is harder and more brittle). **Chrysotile** (or "white asbestos"), which is mined in Canada and the U.S.S.R., is a serpentine form and is the commonest commercial type of asbestos used in the U.S. nowadays. **Crocidolite** (or "blue asbestos") and **amosite** (or "brown asbestos") are both amphiboles which are mined in South Africa, and were used extensively in the U.S. during the 1940's - 1960's.

Persons at risk of developing asbestos-related diseases include the following:

- **Shipyard workers —** some 12 million U.S. Naval Shipyard workers were exposed to asbestos between 1941 and 1976.
- **Insulators**, **pipefitters** and **construction workers**.
- **Brake handlers** and **auto-mechanics**.
- Spouses and children of asbestos workers who received "indirect exposure" to asbestos.
- Persons who live and work "downstream" from asbestos mines and mills.
- **Persons exposed to WTC dust on 9/11/01 —** asbestos fibers were detected in BAL from a NYC firefighter with ILD who was exposed to WTC dust.

**Non-Malignant Asbestos-Related Diseases:** These may affect the lungs and/or the pleura:

- **Parietal pleural plaques:** These are bilateral, circumscribed areas of fibrosis of the parietal pleura overlying the chest wall and diaphragm. Rarely, pleural plaques involve the visceral pleura within the interlobar fissures. Pleural plaques may become calcified. Macroscopically, plaques resemble "sugar-frosting" on a cake. Microscopically, they are composed of dense, hyalinized collagen arranged in a "basket-weave" pattern. Plaques are asymptomatic lesions. Although the pathogenesis of pleural plaques is not known, pleural mesothelial cells and macrophages appear to play a role, since cultured mesothelial cells and pleural macrophages stimulated with asbestos secrete cytokines and growth factors.

- **Benign asbestos pleural effusions:** These are usually unilateral serous effusions which are not associated with underlying malignancy. However, they frequently recur and may eventually produce diffuse fibrosis of both the visceral and parietal pleura. **These are extremely rare lesions**. They are due to the irritant effect of asbestos fibers on the pleural cavity.

- **Diffuse visceral pleural fibrosis:** This is a frequent concomitant of underlying parenchymal asbestosis.

- **Asbestosis:** This term refers to asbestos-induced diffuse interstitial pulmonary fibrosis. In common with nearly all asbestos-related diseases, asbestosis has a tendency to afflict the lower regions of the chest more than the upper regions. Histologically the lesion is characterized by diffuse peribronchiolar and perialveolar fibrosis associated with the presence of asbestos bodies (i.e., coated asbestos fibers) and/or uncoated asbestos fibers. **Asbestos bodies** are typically dumbbell-shaped, segmented structures which are coated with ferric iron, ferritin and a mucopolysaccharide. They have a central, translucent, asbestos-containing core. **Asbestos bodies are not specific for asbestosis and, indeed, are found in nearly all normal city-dwellers**. However, the concentration of asbestos-bodies in the lungs of asbestos workers is approximately one thousandfold-to-ten thousandfold greater than that detected in the lungs of normal individuals. Severe cases of asbestosis involve all the lobes of both lungs, with progression to the typical features of a honeycomb lung.

- **Interstitial pneumonitis:** This usually manifests as a so-called ***desquamative interstitial pneumonitis*** **(*DIP*)**, in which there are prominent aggregates (or "spillover") of alveolar macrophages within the alveolar spaces.

- **Progressive massive fibrosis.**

- **Caplan's syndrome:** This association with rheumatoid arthritis does not occur as frequently as in CWP.

**<u>Clinical Features of Asbestosis</u>:**
- Progressive exertional dyspnea.
- Bilateral basal rales (i.e., crackling sounds) upon chest auscultation.
- Irregular opacities in both lower lobes on chest X-rays.
- Finger clubbing in advanced cases.
- *Cor pulmonale* and *congestive cardiac failure* in severe cases.

**<u>Immunologic Reactions in Asbestosis</u>:** A variety of immunologic abnormalities have been described in association with asbestosis:
- Increased proportions of helper T cells in the blood and lungs.
- Increased secretion of **cytokines** and **growth factors for fibroblasts** by

alveolar macrophages from asbestosis patients (i.e., PDGF, TNF-α, IL-1, fibronectin, IGF-1, and TGF-β).

- Increased MHC class II antigen expression on alveolar macrophages.
- Increased secretion of **oxygen radicals** by alveolar macrophages (i.e., superoxide anion, hydroxyl radical and $H_2O_2$), and **reactive nitrogen species** (especially nitric oxide radical and peroxynitrite anion).

**Malignant Asbestos-Related Diseases:**

- **Asbestos-related bronchogenic carcinoma**. **This is the most common neoplasm encountered in asbestos workers** (i.e., ± 20% of such individuals in some published series have died of lung cancer). Although lung cancer can occur in the absence of coexistent asbestosis, the risk of developing lung cancer is approximately doubled in workers who have asbestosis. Bronchogenic carcinomas which develop in asbestotic lungs also represent examples of so-called *scar cancers*. **Asbestos workers who smoke also have a heightened predisposition towards lung cancer**. Thus, the risk of developing lung cancer in asbestos workers who smoke is about fiftyfold greater than the risk of developing lung cancer amongst the non-smoking general U.S. population. Non-smoking asbestos workers have only a modest (i.e., fivefold) increased risk of developing lung cancer when compared with the non-smoking general U.S. population. **Thus, the effects of asbestos and smoking are multiplicative**. It should be noted that smoking does not heighten the risk of developing malignant mesothelioma. All histologic varieties of bronchogenic carcinoma are found in asbestos workers. The clinical features and prognosis of lung cancer are no different from those encountered in non-asbestos-exposed situations. Although the mechanisms of asbestos-induced carcinogenesis are poorly understood, it appears that asbestos may act either as an initiator and/or a promoter of carcinogenesis. In this regard, it is of interest that asbestos fibers can bind to DNA and RNA, and can also cause DNA strand breaks. Asbestos fibers also can activate **early-response genes** (e.g., *c-fos* and *c-jun*) and also can activate genes involved in **signal transduction signaling pathways** (e.g., *ERK1/ERK2*).

- **Malignant pleural mesothelioma: This is an exceedingly rare neoplasm in the general U.S. population** (i.e., the incidence in North America is about 1-2 per 100,000 persons). By contrast, ± 3-10% of asbestos workers' deaths are due to malignant mesothelioma. The disease usually develops about 20-50 years after initial asbestos contact. Patients present with unilateral, hemorrhagic, recurrent pleural effusions associated with intractable chest pain and progressive dyspnea. The tumor tends to totally encase the lung on one side, with obliteration of the pleural space. Patients experience a type of "death by suffocation". Metastases are common. The patient's prognosis is dismal.

- **Malignant peritoneal mesothelioma:** About one third of all malignant mesotheliomas arise in the peritoneal cavity. Numerous tumor implants invade the surfaces of most of the abdominal viscera (e.g., liver, stomach and bowel). Massive, recurrent ascites is the major clinical feature. As with pleural involvement, the prognosis is poor - most patients are dead within 18 months of diagnosis.

  The histologic varieties of malignant mesothelioma are identical for both pleural and peritoneal mesotheliomas:
  - ***Epithelial*** — a tubulo-papillary pattern is noted.
  - ***Sarcomatoid*** — a spindle cell pattern is observed.
  - ***Mixed epithelial and sarcomatoid pattern.***

  **The histologic diagnosis of diffuse malignant mesothelioma sometimes can be difficult to establish**. ***The epithelial variety may be confused with some types of metastatic adenocarcinoma to the pleura***, and both immunohistochemical and histochemical markers may be needed to establish an accurate diagnosis. It should be noted that the neoplastic cells in cases of diffuse malignant mesothelioma tend to stain positively with immunohistochemical markers for vimentin, calretinin and certain cytokeratin proteins. Since the tumor cells also frequently contain large amounts of the proteoglycan, hyaluronate, they stain positively with histochemical stains for acid mucopolysaccharide (e.g., alcian blue and a biotinylated probe for hyaluronate).

- **Other asbestos-related cancers:** Some studies have shown an increased frequency of other cancers in asbestos workers. However, the role of asbestos exposure in the causation of these cancers is not as clearly established as is the case with diffuse malignant mesothelioma and lung cancer:
  - ***Carcinomas of the oropharynx, larynx, esophagus, colon, and rectum***.
  - ***Lymphoid neoplasms***: These tumors are mainly of **B-cell lineage** (especially non-Hodgkin's lymphomas, myeloma, and chronic lymphocytic leukemia).

**Mixed Dust Pneumoconioses:** People exposed to **mixtures of silica, asbestos and/or coal dust** may develop a "mixed" fibrotic pattern with features of ***silicosis***, ***CWP*** or ***asbestosis***. This is seen in workers exposed to sheet silicates (e.g., talc, mica, slate, graphite or kaolin). The fibrosis results from the presence of quartz or asbestos contaminants in these dusts. The scarring frequently has a stellate configuration.

**Berylliosis:** Beryllium has been used in the manufacture of fluorescent lamps and is now encountered in the electronics, aerospace, nuclear energy and ceramics industries. Host factors appear to play a role in beryllium susceptibility since only 2-5%

of occupationally exposed people will develop berylliosis. There are two forms of berylliosis:

- **Acute berylliosis:** This entity, which is rarely encountered nowadays, is characterized by a severe, acute allergic pneumonitis, rhinitis, pharyngitis and tracheobronchitis. The lungs exhibit a severe acute bronchopneumonia which frequently undergoes organization and fibrosis. It can prove fatal.

- **Chronic berylliosis:** This is the more frequent variety. **It resembles sarcoidosis in certain respects** (e.g., non-caseating epithelioid cell granulomas occur in the lungs, liver, skin, kidney, spleen and lymph nodes). However, the ***Kveim test is always negative*** in berylliosis. Most cases progress to interstitial pulmonary fibrosis. **Chronic berylliosis is a classic example of a *type IV hypersensitivity reaction***. Patients' blood and lung lymphocytes proliferate and generate cytokines, when challenged with beryllium salts *in vitro*. Patients frequently manifest positive delayed hypersensitivity cutaneous reactions to beryllium salts. **Beryllium may also be a carcinogen** — there is a twofold increased risk of developing lung cancer in beryllium workers, when compared with the general U.S. population.